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Core Functionalization of Hollow Polymer Nanocapsules

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Hollow nanoscale polymer capsules have found wide applications in drug delivery and catalysis.[1] Polymer nanocapsules can be prepared via self-assembly or through the use of a sacrificial nanoscale template. In the former strategy, amphiphilic diblock copolymers that self-assemble into core−shell micelles are cross-linked in their exterior block, followed by removal of the core.[2] In the latter approach, a nanoparticle is used either as a template for the inititation of polymerization, or as a support on which polymers are adsorbed. Cross-linking of the resultant polymer shell followed by removal of the template generates the nanocapsule.[3] The use of nanocapsules and related materials requires control over cargo entry and exit and installation of diverse chemical functionality in the capsule interior. Despite the diversity of methods for nanocapsule preparation, methods for efficiently functionalizing the core of hollow nanocapsules are scarce.[2c,i]

We report here a versatile and modular approach for the synthesis of hollow polymeric capsules that can be readily and diversely functionalized in the core. The block copolymer (**poly1**)$_{30}$-*block*-(**poly2**)$_{30}$, which is grafted on the surface of gold nanoparticles serves as the precursor for polymer capsules (Figure 1). This

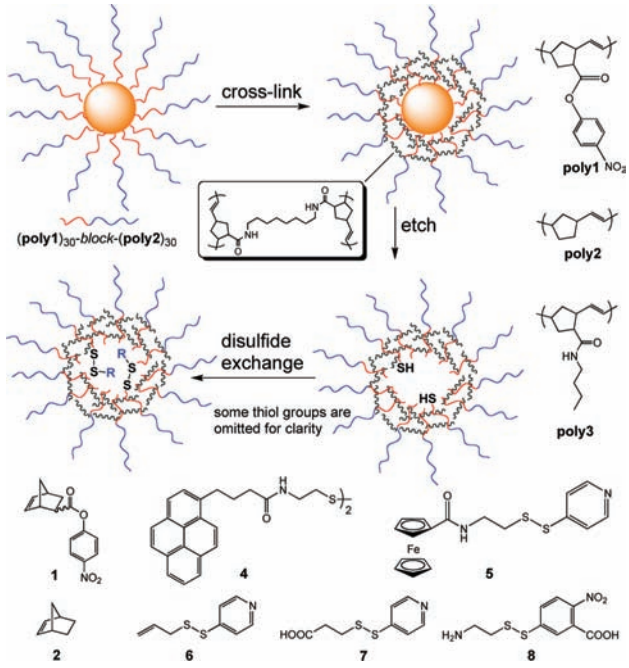

Figure 1. Template based nanocapsule synthesis followed by core functionalization.

polymer is synthesized using previously reported procedures for the radial surface initiated ring-opening metathesis polymerization (ROMP)[4] of a thiol terminated norbornene anchored on a gold nanoparticle.[5] The molecular weight of the linear block copolymer prior to cross-linking was determined using MALDI-ToF MS (M_n = 7704, M_w = 9399, PDI = 1.22). ^{1}H NMR integration of the linear polymer indicates the fraction of **poly1** is 45%, very close to the target value 50%.[6] The interior block, (**poly1**)$_{30}$, contains an activated ester which was cross-linked using 1,8-diaminooctane (0.5 equiv of diamine relative to the ester). The exterior block, (**poly2**)$_{30}$, renders the polymer soluble in organic solvents and minimizes the formation of interparticle cross-links during the reaction with diaminooctane. The extent of cross-linking was determined to be >90% (Supporting Information, SI). Nanocapsules were obtained by oxidatively etching the gold nanoparticles using sodium cyanide, which concomitantly oxidizes the polymer thiol termini to disulfides. The disulfides can be reduced with tributylphosphine to provide nanocapsules with functionalizable thiol groups in the core. This work provides core functionalized capsules that are soluble in organic solutions, complementing previously reported core functionalized nanocapsules that are water-soluble.[2i]

Dynamic light scattering (DLS) of a solution of nanocapsules (containing a disulfide core) indicates that the average diameter of hollow capsules in THF is 107 ± 29 nm (Figure 2a), while TEM

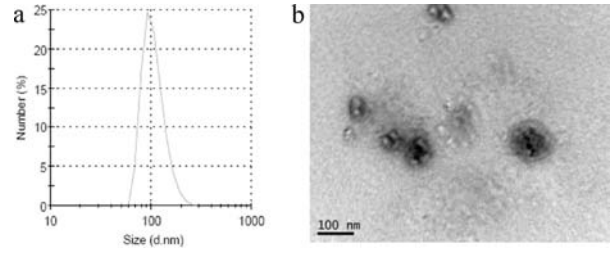

Figure 2. (a) DLS measurement of nonfunctionalized nanocapsules; (b) TEM image of nanocapsules functionalized with **5**.

images (SI, Figure S5) indicate slightly larger diameters (143 nm), presumably arising from capsule flattening on the TEM grid. Thin films of different polymers were spin-coated onto glass slides, and the water contact angles of these surfaces were measured. The advancing water contact angle of the capsule coated slides (80.5°) lies between the values for (**poly2**)$_{60}$ (87.6°) and butylamine-quenched thiol-terminated (**poly1**)$_{30}$-*block*-(**poly3**)$_{30}$ (73.3°),[7a] suggesting that the cross-linked polyamide block is partly shielded from water on the spin-coated surface.

With the capsules in hand, we turned our attention to the functionalization of the capsules. The core was functionalized with pyrene using a disulfide exchange reaction with **4**. The pyrene functionalized capsule exhibits a strong excimer emission at 478 nm (Figure 3, trace b), in addition to a monomer emission at 378 nm, indicating close proximity betweeen adjacent disulfide linked pyrene moieties.[8] Only monomer emission was observed (Figure 3, trace c) after the capsules were treated with tributylphosphine, which cleaves the disulfide linkages to liberate pyrene. Dialysis of the phosphine treated capsules provided capsules with no fluorscence emission (Figure 3, trace d). These results indicate that the

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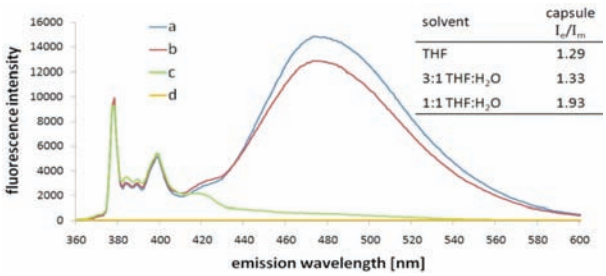

Figure 3. Emission spectra in THF of (a) compound **4**; (b) nanocapsules functionalized with **4**; (c) nanocapsules functionalized with **4** after treatment with tributylphosphine; (d) nanocapsules functionalized with **4** after treatment with tributylphosphine followed by dialysis. $\lambda_{excitation} = 338$ nm. Inset table shows the solvent dependence of the excimer (I_e @ 478 nm) to monomer (I_m @ 378 nm) for nanocapsules functionalized with **4**.

pyrene moieties in nanocapsules functionalized with **4** are covalently attached to the capsules and not physically adsorbed or trapped within the polymer shell. The ratio of excimer to monomer emission increased from 1.29 to 1.93 as the water content of the solution increased from 0% to 50%. In contrast, the pyrene terminated linear polymer (**poly1**)$_{30}$-*block*-(**poly3**)$_{30}$ had an excimer/monomer ratio of 0.75, and this ratio did not increase when water was added.[7b] These data suggest that increasing water content may induce capsule constriction, resulting in a closer packing of pyrene groups within the core.

Core functionalization efficiency was evaluated using nanocapsules functionalized with **5**. The Fe/S molar ratio for these capsules was determined using inductively coupled plasma spectrometry. A value of 0.399 was measured, indicating that 80% of the thiols were functionalized with ferrocene. TEM images of the ferrocene-modified capsules indicated regions of increased electron density toward the capsule cores (Figure 2b).[9]

To probe applications of these capsules as potential drug delivery vehicles or as materials for chemical separations, alizarin red S (ARS), an anionic dye, and methylene blue (MB), a cationic dye, were used as model compounds to study the encapsulation and release of small molecules. Capsules functionalized with allyl, amine, or carboxylic acid groups were prepared using disulfides **6**, **7**, and **8**, respectively. After incubating the capsules (1 mg/mL in CH_2Cl_2) with an aqueous solution of ARS (14.6 mM) or MB (2.7 mM) at room temperature for 1 h, the absorbance of the dichloromethane layer was obtained to determine the amount of dye extracted into the organic layer (Figure 4a). ARS, which is poorly

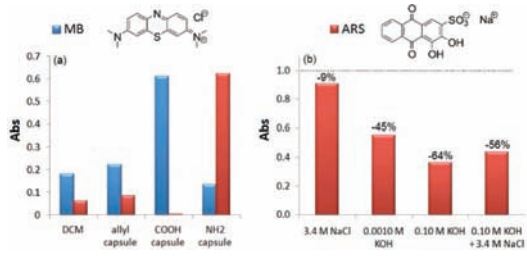

Figure 4. (a) Postextraction MB (blue) and ARS (red) absorbance values of dichloromethane layers containing no capsules (DCM), allyl, carboxylate, or amino functionalized capsules. (b) Absorbance of dichloromethane layer containing encapsulated ARS after stirring with different aqueous solutions for 1 h. Absorbances at 656 and 424 nm were monitored for MB and ARS, respectively.

soluble in dichloromethane, is efficiently extracted into the organic layer by the amino capsule (final concentration in CH_2Cl_2 150 μM). In contrast, very little uptake is observed with the carboxy and allyl functionalized capsules. Conversely, the carboxylate capsule selectively extracts the cationic MB into the organic layer (final concentration in CH_2Cl_2 2.1 μM).

Release of sequestered dyes from the nanocapsules can be induced by an appropriate chemical stimulus. Capsules containing ARS were incubated with different aqueous media (Figure 4b). The release of ARS into pure water is negligible, and most of the dye remains in the organic layer even at high salt concentrations. Release can be triggered by using a basic solution, which presumably deprotonates the capsule amine groups, reducing the electrostatic attraction for ARS. Adjusting the base or salt concentration can further modulate the amount of dye that is released. Analogously, the release of MB can be triggered under acidic conditions (SI, Figure S9).

The versatile synthetic approach reported here provides opportunities to prepare nanocapsules with a variety of functional groups in the core. The observation of pyrene excimers, the TEM images of ferrocene functionalized capsules, and the selective extraction of organic insoluble charged dyes are all consistent with some degree of sequestration of the disulfide moieties away from the capsule exterior, although partial "flipping" of the disulfide linkages toward the exterior cannot be unequivocally ruled out. The groups in the core impart diverse functions to the capsules, exemplified here by the selective extraction of dyes. Cargo release can be induced by an appropriate stimulus, in this case a change in acidity or disulfide reduction. The ability to control core selectivity using a common starting material highlights the modularity of this synthetic approach to core functionalized capsules.

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Supporting Information Available: Experimental procedures for ligand and monomer synthesis and characterization, nanoparticle and polymer analysis, and NMR and MALDI spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(6) Details of polymer characterization are provided in the Supporting Information.
(7) (a) The **poly3** block in this copolymer is derived from treatment of **AuNP**-(**poly1**)$_{30}$-*block*-(**poly2**)$_{30}$ with butylamine. (b) The pyrene terminated copolymer is obtained by cyanide etching, phosphine reduction, and reaction with excess **4**.
(8) The fluorescence spectrum of the pyrene disulfide **4** (Figure 3, trace a) consists primarily of the excimer emission.
(9) A clear core−shell morphology is visible by TEM by preparing capsules in which the cross-linking region is on the exterior, followed by N-alkylation of the amide nitrogens with a ferrocene derivative (Figure S7).

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